

## Transfusion-related acute lung injury; clinical perspectives

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Transfusion-related acute lung injury (TRALI) was introduced in 1983 to describe a clinical syndrome seen within 6 h of a plasma-containing blood products transfusion. TRALI is a rare transfusion complication; however, the FDA has suggested that TRALI is the leading cause of transfusion-related mortality. Understanding the pathogenesis of TRALI will facilitate adopting preventive strategies, such as deferring high plasma volume female product donors. This review outlines the clinical features, pathogenesis, treatment, and prevention of TRALI.

**Key Words:** Acute lung injury, Diagnosis, Etiology, Prevention and control, Prognosis, Transfusion reaction.

Since transfusion was introduced, the associated risks, including transfusion-transmitted infection and incompatibility, have decreased with improved quality [1]. Although the frequency of many complications has decreased, transfusion-related acute lung injury (TRALI) has become one of the major complications associated with transfusion. TRALI is a potentially fatal blood-product transfusion complication that presents as acute hypoxemia and noncardiogenic pulmonary edema.

The first case of TRALI was reported in the 1950s [2]. Although TRALI has been termed a pulmonary hypersensitivity reaction, pulmonary infiltrate associated with transfusion reaction, and fulminating noncardiogenic pulmonary edema [3], the diagnostic term TRALI was first suggested by Popovsky et al. [4]

in 1983.

### Definition and Epidemiology

TRALI is the leading cause of transfusion-related mortality in the United States. TRALI was defined based on clinical and radiological parameters at the 2004 Consensus Conference, as newly developed acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) within 6 h of a blood product transfusion (Table 1) [3]. The 6 h time window was chosen based on the opinion of an expert panel. *Suspected TRALI* was defined as fulfillment of the definition of TRALI without another ALI risk factor. Because the characteristics of TRALI are difficult to distinguish from those of ALI due to other causes, *possible TRALI* has been suggested to allow for the presence of other ALI risk factors. The conventional definition of TRALI included cases of ALI that develop within 6 h of transfusion, but transfusion is an ALI risk factor for 6–72 h. Thus, delayed TRALI includes delayed onset TRALI after transfusion [5].

TRALI occurs in up to 15% of transfused patients [6], but other reports estimate the incidence of TRALI at approximately 0.1% of transfused patients [7,8].

Although the true incidence of TRALI is unknown, it is likely under-diagnosed and under-estimated, primarily due to poor recognition of the disease [8]. Several studies have reported inci-

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**Table 1.** Definition of TRALI

Suspected TRALI	
Acute onset within 6 h of blood transfusion	
PaO <sub>2</sub> /FIO <sub>2</sub> < 300 mmHg, or worsening of P/F ratio	
Bilateral pulmonary infiltrates on chest radiograph	
No sign of hydrostatic pulmonary edema (pulmonary arterial occlusion pressure ≤ 18 mmHg or central venous pressure ≤ 15 mmHg)	
No other risk factor for acute lung injury	
Possible TRALI	
Same as for suspected TRALI, but another risk factor present for acute lung injury	
Delayed TRALI	
Same as for (possible) TRALI and onset within 6–72 h of blood transfusion	

PAOP: pulmonary arterial occlusion pressure, CVP: central venous pressure, TRALI: transfusion-related acute lung injury.

dence ranges of 1 in 7,900 units of fresh frozen plasma (FFP) to 1 in 432 units of whole blood [9,10]. In addition, the incidence of TRALI depends on the patient population, and a higher incidence of TRALI is observed in critically ill patients [11]. Historical estimates for TRALI-associated mortality range from 5 to 8% [12], but up to 60% of critically ill patients die from TRALI [13].

### Risk factors

Specific risk factors for TRALI can be divided conceptually into recipient-related risk factors and transfusion-related risk factors [14].

#### Recipient-related risk factors

Many comorbidities have been suggested as TRALI risk factors, including end-stage liver disease, coronary artery bypass graft, hematological malignancies, massive transfusion, mechanical ventilation, sepsis, and heavy alcohol consumption [14]. Critical illness is one of the highest risks for TRALI [11,13]. A large database review of 11 million elderly patients in the United States revealed that TRALI rates are higher in patients receiving a transfusion, including platelets or plasma [15]. TRALI incidence increase as the number of units transfused increases. A review also identified that elderly female Caucasians 65–79-years-old with a 6-month history of post-inflammatory pulmonary fibrosis and tobacco use have a greater chance of developing TRALI [15].

#### Transfusion-related risk factors

Immunoglobulin [16] and stem cell preparations [17] are also associated with TRALI. A case-control study enrolled 89 patients with TRALI and 164 controls. The study revealed that a higher TRALI odds ratio (OR) is associated with plasma from

female donors (OR, 4.5; 95% confidence interval [CI], 1.85–11.2) and a greater number of transfusions (OR, 4.5; 95% CI, 2.4–8.4). [18] Blood products including high-plasma-volume (platelet concentrates, whole blood, and FFP) have been associated with a higher incidence of TRALI [13]. High loading of anti-human neutrophil antigen antibody has also been associated with TRALI [18]. In contrast, the presence of anti-human leukocyte antigen (HLA) class II or anti-HLA class I antibodies is not associated with TRALI.

The age of a blood product has been suggested to increase the risk for TRALI [19]. Storing red blood cells (RBCs) results in a number of morphological and biochemical alterations known as RBC storage lesions. However, two studies failed to reveal blood age as a risk factor for TRALI [13,18].

## Pathogenesis

### Two-hit model

A two-hit hypothesis has been suggested for developing TRALI [20]. The first hit involves neutrophil sequestration and priming in the pulmonary endothelium, which precedes transfusion. Endothelial cells are thought to be responsible for both neutrophil sequestration and priming. The second hit is caused by activation of the endothelium and neutrophils by mediators in the transfused blood, resulting in capillary leakage and pulmonary edema. The second hit differs in antibody-mediated TRALI and non-antibody-mediated TRALI. Non-antibody-mediated TRALI is caused by the accumulation of proinflammatory mediators during storage of blood products and possibly by ageing of RBCs and platelets [21], whereas antibody-mediated TRALI or immune TRALI is caused by passive transfusion of HLA or human neutrophil antigen (HNA) and corresponding antibodies from the donor directed against recipient antigens [22]. Donor anti-leukocyte antibodies interact with recipient neutrophils, monocytes, and/or the pulmonary endothelium [14]. Bioactive lipids and other factors in transfused blood act as biological response modifiers in patients with non-antibody-mediated TRALI. The proportions of antibody-mediated vs. non-antibody-mediated TRALI cases remain unclear. A systemic review showed that 86% of TRALI cases are associated with leukocyte antibodies [23].

### Threshold model

The two-hit hypothesis explains the occurrence of TRALI in high-risk patients. However, this hypothesis does not fit TRALI that develops in healthy recipients; the threshold model has been proposed to explain these cases [24]. This model generally agrees that two hits are needed to develop TRALI. However, the

threshold model assumes that TRALI can occur when the second hit is so strong that an initial priming event is not needed. In other words, a large quantity of antibody (second hit) can cause TRALI in a recipient with no previous predisposition, such as in healthy individuals.

### Clinical presentation and diagnosis

TRALI presents as sudden onset of respiratory difficulties during or shortly after transfusion. Hypoxemia and lung infiltrates are detected on chest X-rays in almost all patients with TRALI, and half of patients show a pinkish, frothy sputum [25]. Tachypnea, tachycardia, and elevated airway pressure are frequently observed. Fever, hypotension, and cyanosis occur in less than one-third of patients with TRALI.

Confirming hypoxemia, obtaining a chest X-ray, and evaluating vital signs are required to diagnose TRALI.

No laboratory test is specific for diagnosing TRALI. The greatest change is a transient drop in peripheral neutrophil count (possibly due to neutrophil sequestration in the pulmonary vasculature). Leucopenia occurs in 35% of patients after transfusion with an antibody-containing blood product [26].

TRALI should be distinguished from pulmonary edema due to other causes. Hemolytic and septic transfusion reactions present similarly to TRALI. Anaphylaxis can cause respiratory insufficiency similar to that of TRALI, but airway signs and symptoms are more common in patients with anaphylaxis. ALI/ARDS should be distinguished from TRALI in patients with risk factors for ALI/ARDS prior to a transfusion.

Transfusion-associated circulatory overload (TACO) is another cause of transfusion-related respiratory insufficiency (Table 2) [27]. Impaired myocardial function and rapid and aggressive fluid therapy are suggested risk factors for TACO. TRALI is more likely to be associated with signs and symptoms of inflammation, including fever, hypotension, and an exudative pulmonary infiltrate. In contrast, TACO is more likely to be associated

with findings suggestive of cardiac dysfunction and/or volume overload.

### Treatment

No specific treatment exists for this syndrome. Corticosteroids have been used for ALI/ARDS, but the results are inconsistent. Routine use of corticosteroids in patients with TRALI is not advocated, although a successful case has been reported [28].

The transfusion should be stopped immediately if TRALI is suspected. The blood bank should be notified of the event to initiate a transfusion reaction evaluation to protect further unexpected victims.

Management of TRALI is supportive. Providing oxygen supplementation is the central management approach for hypoxemia. Limited evidence is available for managing patients with TRALI using mechanical ventilation [29], and it is logical to apply a lower tidal volume in patients with ARDS from other causes. There is a case report of applying extracorporeal membrane oxygenation in a patient with severe TRALI [30].

### Prognosis and prevention

Mortality due to TRALI is 5–10%, in contrast to ARDS [31]. However, 90-day mortality associated with TRALI can reach 47% in critically ill populations [13]. Long-term pulmonary function in TRALI survivors seems to be similar to that of patients who have never experienced TRALI, and no apparent late complications, such as fibrosis or other structural damage to the lung parenchyma occur as a result of TRALI [13]. The clinical course of patients with TRALI is suggested by quick resolution (~2 days) of hypoxemia.

Cases suspected of TRALI should be promptly reported to the blood bank. The blood bank should investigate all associated donors for the presence of anti-HLA and anti-HNA antibodies to identify donors with these antibodies and prevent them from future donation. This is particularly true if the donor has anti-HNA 3a [32].

In addition, several general blood donor management strategies are in use to reduce the incidence of TRALI [32-38]. First, adherence to current guidelines for utilizing blood components, particularly those for plasma, is mandatory to decrease exposure risk for patients. A restrictive transfusion strategy has been associated with a lower incidence of TRALI compared with that of a liberal transfusion strategy [39]. Clifford et al. [40] reported that patients transfused with greater volumes of blood components develop perioperative TRALI/possible TRALI more frequently than that reported previously. He reported that the overall incidence of TRALI was 22.46 per 100,000 stays. Optimal transfusion guidelines should provide sufficient blood products to

**Table 2.** Distinguishing TRALI from TACO

	TRALI	TACO
Blood pressure	Low-normal	Normal-high
Body temperature	Normal-elevated	Normal
CXR	No vascular congestion	Vascular congestion, pleural effusion
BNP	Low (< 250 pg/ml)	High
PAOP	Low-normal	High
Ejection fraction	Normal function	Abnormal function
Response to diuretics	Inconsistent	Improved
Edema fluid	Transudate	Exudate

TRALI: transfusion-related acute lung injury, TACO: transfusion-associated cardiac overload, CXR: chest X-ray, BNP: B type natriuretic peptide, PAOP: pulmonary artery occluding pressure.

maximize clinical outcomes while avoiding adverse events, such as TRALI. However, no golden transfusion guidelines exist for all patients. Clinicians should consider many factors when deciding to transfuse anemic patients, rather than basing the decision solely on a specified laboratory level. In this respect, Carson et al. [41] demonstrated that liberal blood transfusion approach with a hemoglobin concentration threshold of 90–100 g/L does not affect mortality in a high-risk group of elderly patients with underlying cardiovascular disease or risk factors, compared with that of a restrictive transfusion strategy with a hemoglobin concentration threshold of 70–80 g/L. Therefore, the final decision

to transfuse should incorporate the patient's clinical condition, co-morbidities, and the individual wishes of the patient. Second, donors with little chance to be alloimmunized to leukocytes should receive high plasma volume components (e.g., FFP, plasma frozen within 24 h of phlebotomy [FP-24], plasma, cryo-reduced plasma, apheresis platelets, or whole blood). Third, use pooled solvent detergent-treated plasma as an alternative to FFP. Fourth, test for anti-HLA antibodies in pregnant donors before apheresis of platelets or plasma. In particular, several management strategies including deferral of multiparous female donors are in use to reduce the incidence of TRALI [42].

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